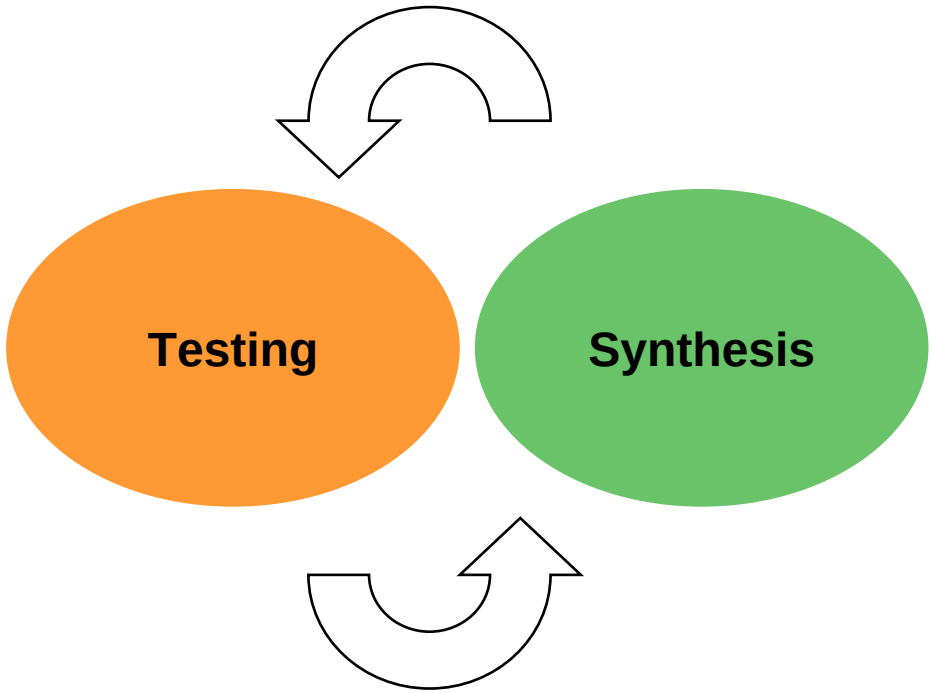
Tools and Methods of Proven Value in Molecular Design

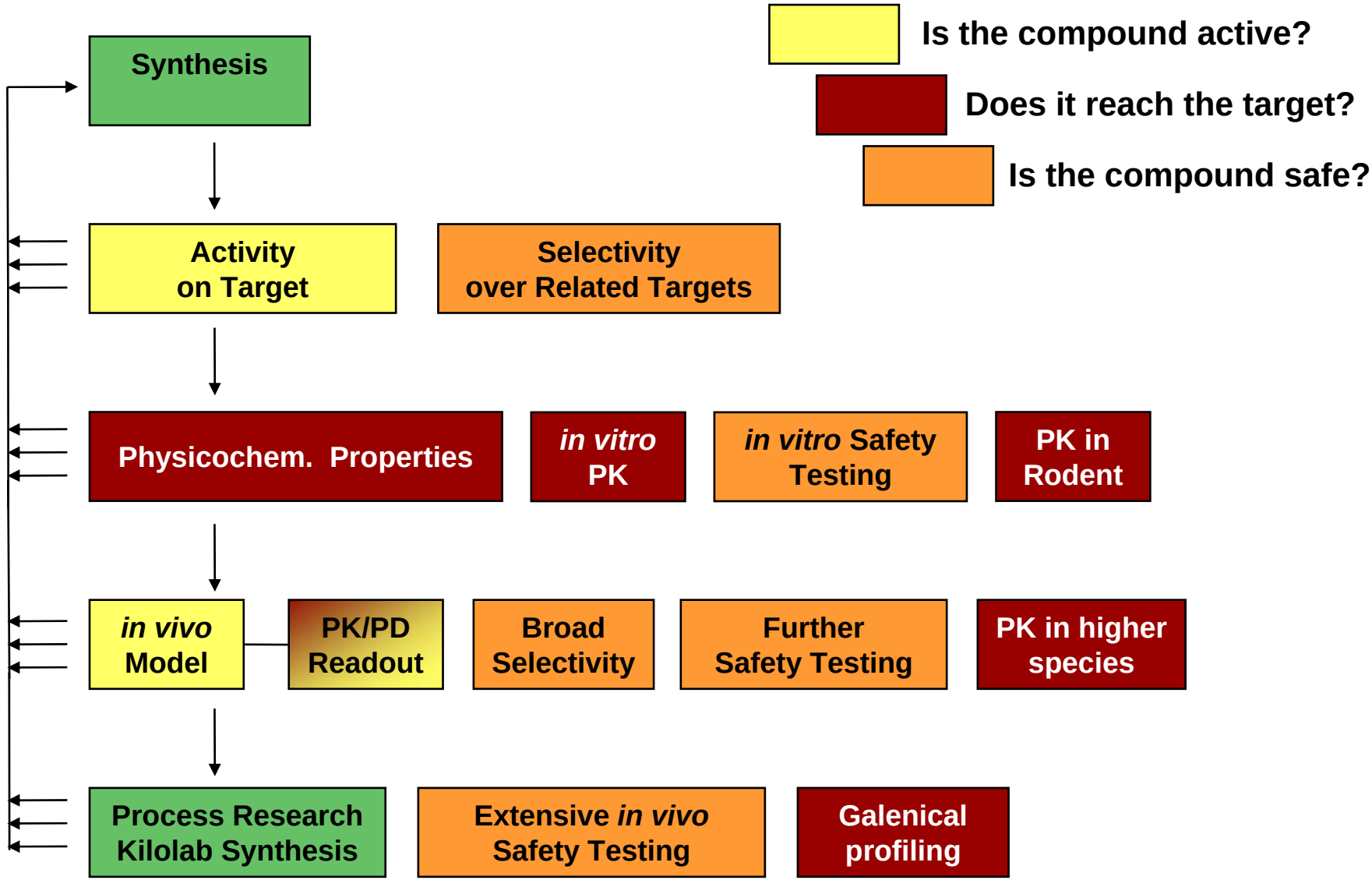
Martin Stahl, June 2007

Medicinal Chemistry
A Core Discipline in Drug Discovery



Synthesis Planning based on New Data

The Parallel Screening Cascade



What are the Tools We Really Need?

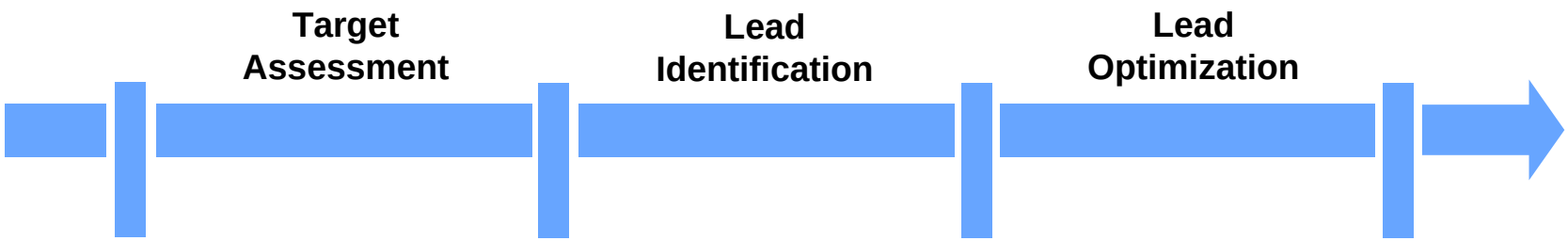
General Considerations

- Computational models should be useful, not beautiful.
- Reducing an idea to practice is an interactive process.
- Know the limits of your calculations.
- Learn as much as possible from experimental data.
- Method development is often not about great ideas, but about solid implementations.

M. Stahl et al., DDT **2006**, *11*, 326-333.

The Computational Toolbox

CAMM Activities Focus on Early Projects



Medicinal chemistry activities

CAMM activities

Feasibility assessment

data collection and model building:
sequences
pharmacophores
x-ray structures
homology models

Focused screening

HTS data analysis

Compound tracking, annotation, multivariate SAR building

Iterative hypothesis generation
design and evaluation of proposals

Some Useful Tools

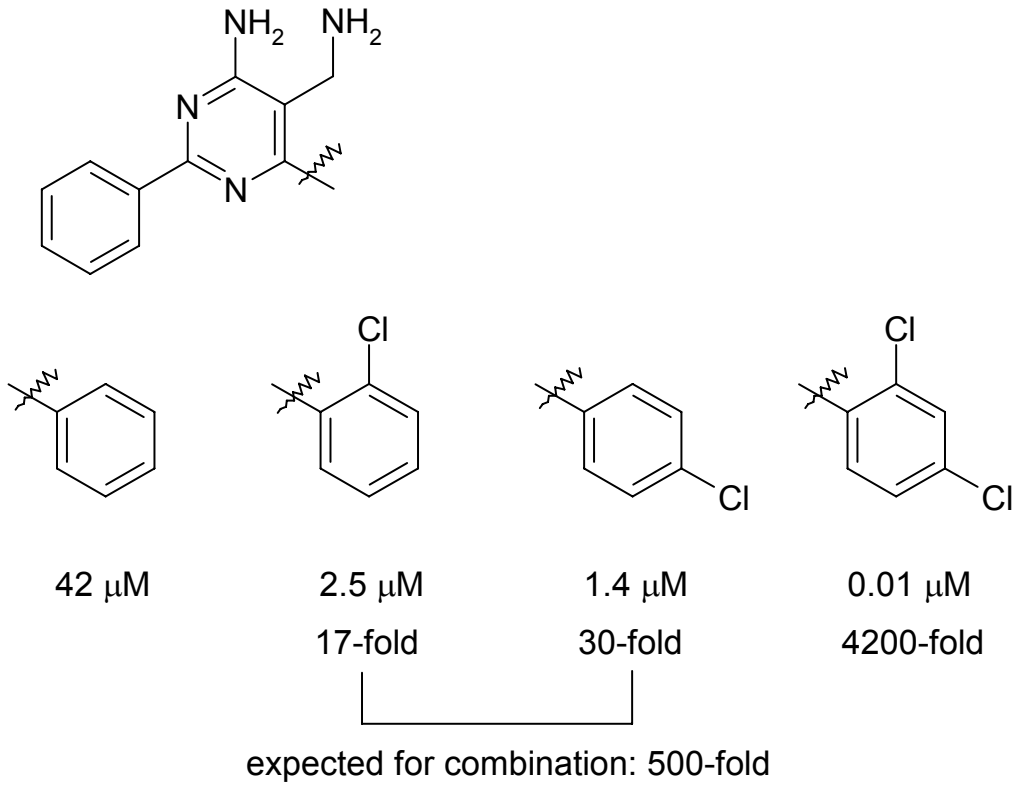
- Molecular Similarity Metrics: Searching, Clustering
- De novo design as an idea generator
- Tools for multivariate data analysis and multiobjective design: from multiple *in vitro* to *in vivo* and from structure to effect/property
- Interactive design: pharmacophore- and structure-based
- Structural databases (PDB, CSD) as a means of improving our knowledge
- Automated docking / structure-based design using proper constraints - fixed fragments, pharmacophores, active site definition
- Target family approaches ("chemogenomics")

Using Structural Databases

A New Tool for Scaffold Hopping

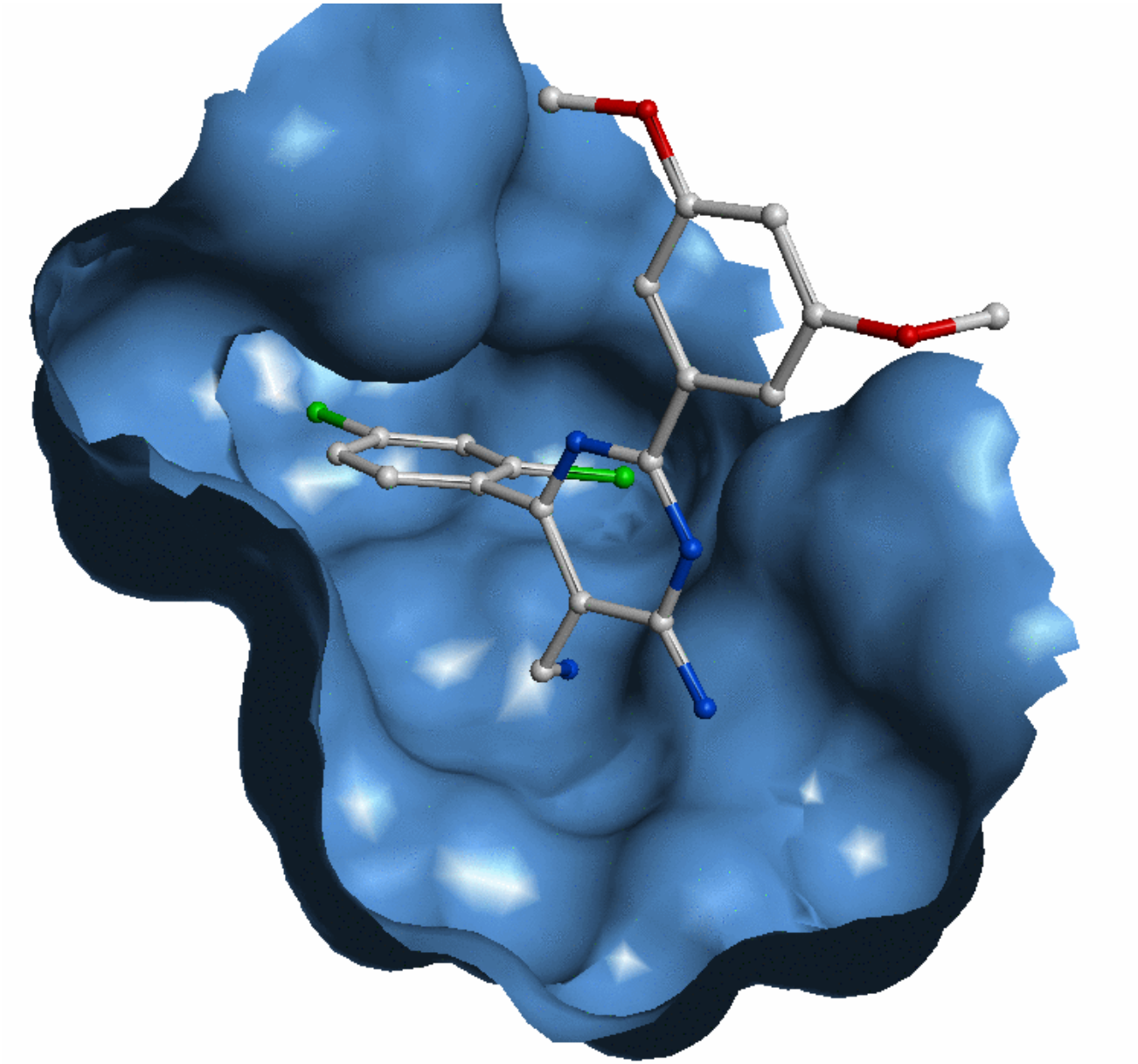
Target Family Approaches

Optimization of Aminomethylpyrimidine DPP-IV Inhibitors

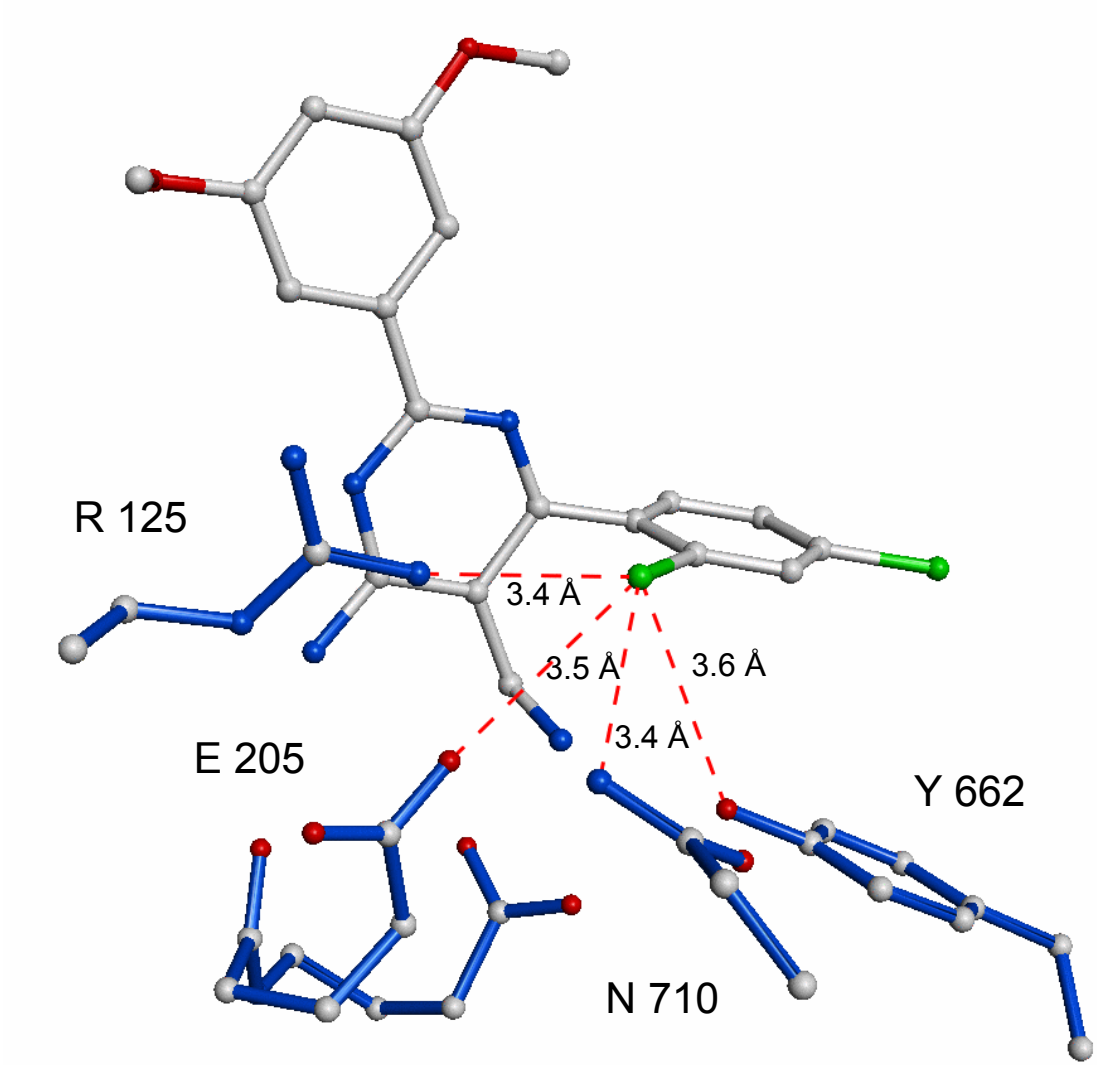


J.-U. Peters et al., BMCL 2004, 14, 1491

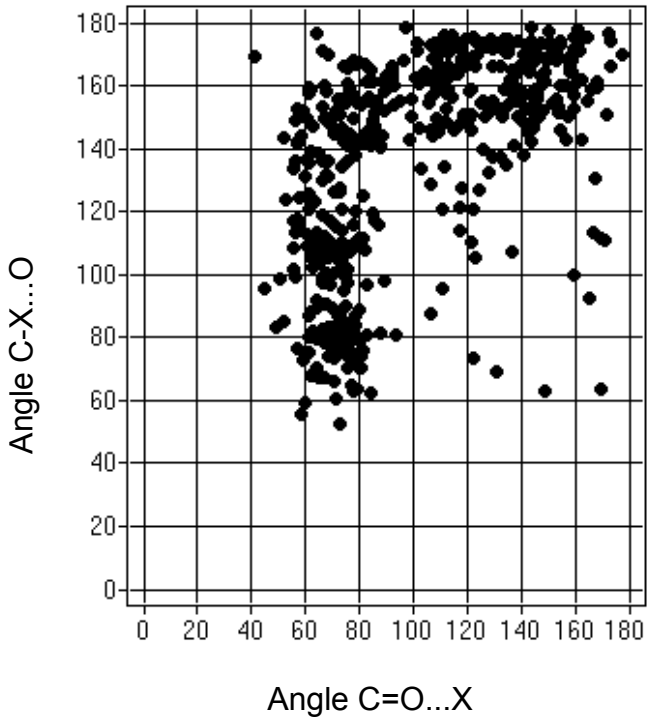
Binding Mode of Aminomethylpyrimidines

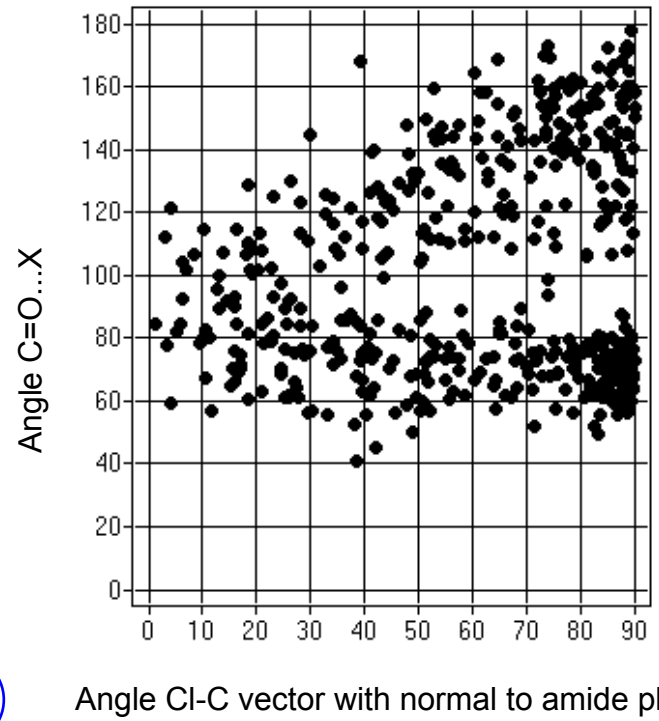


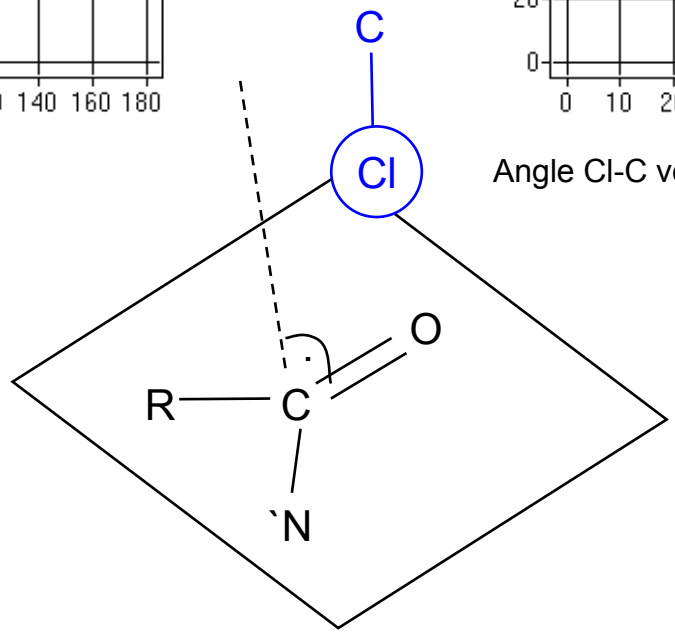
Polar Environment of *ortho*-Cl



Cl-Amide Interactions in the CSD

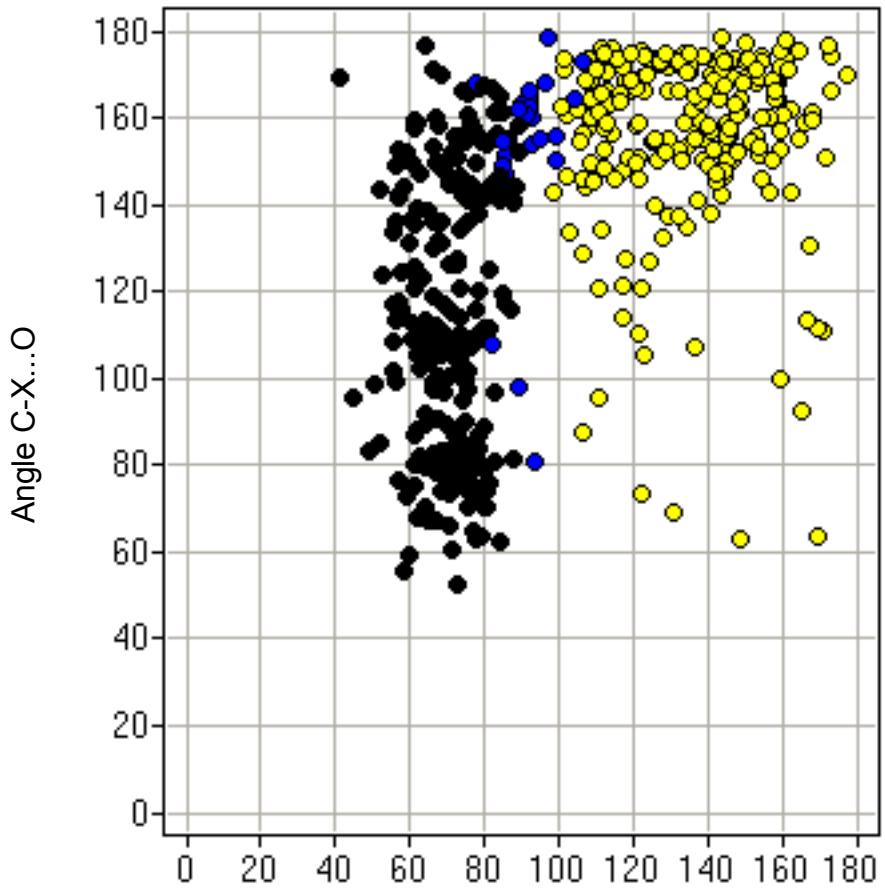


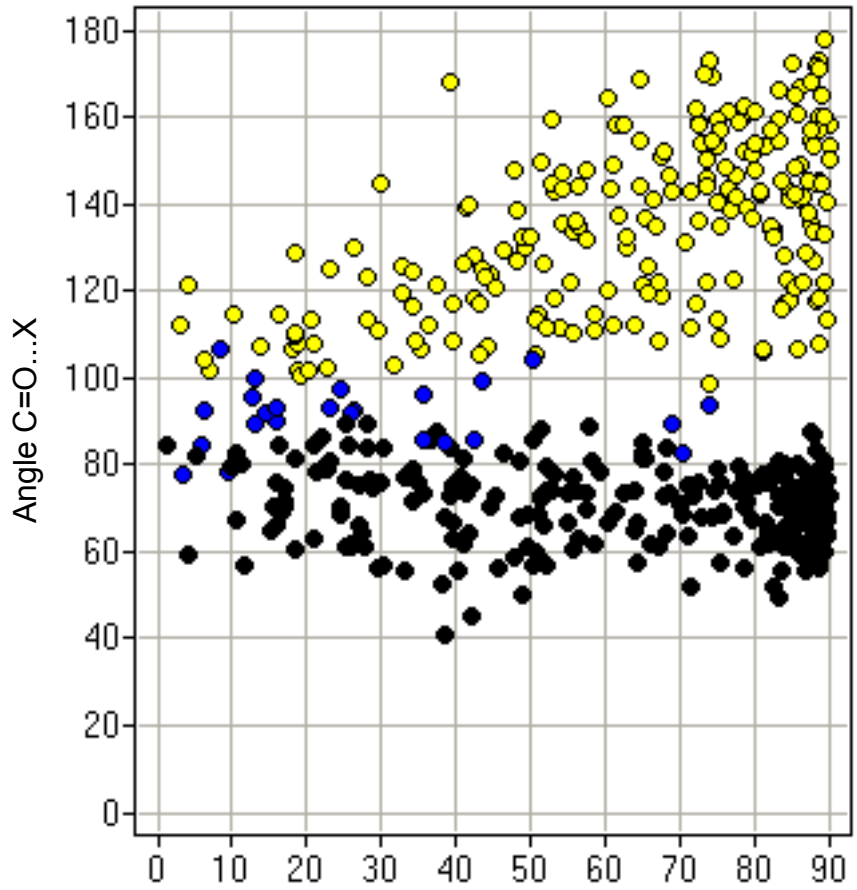




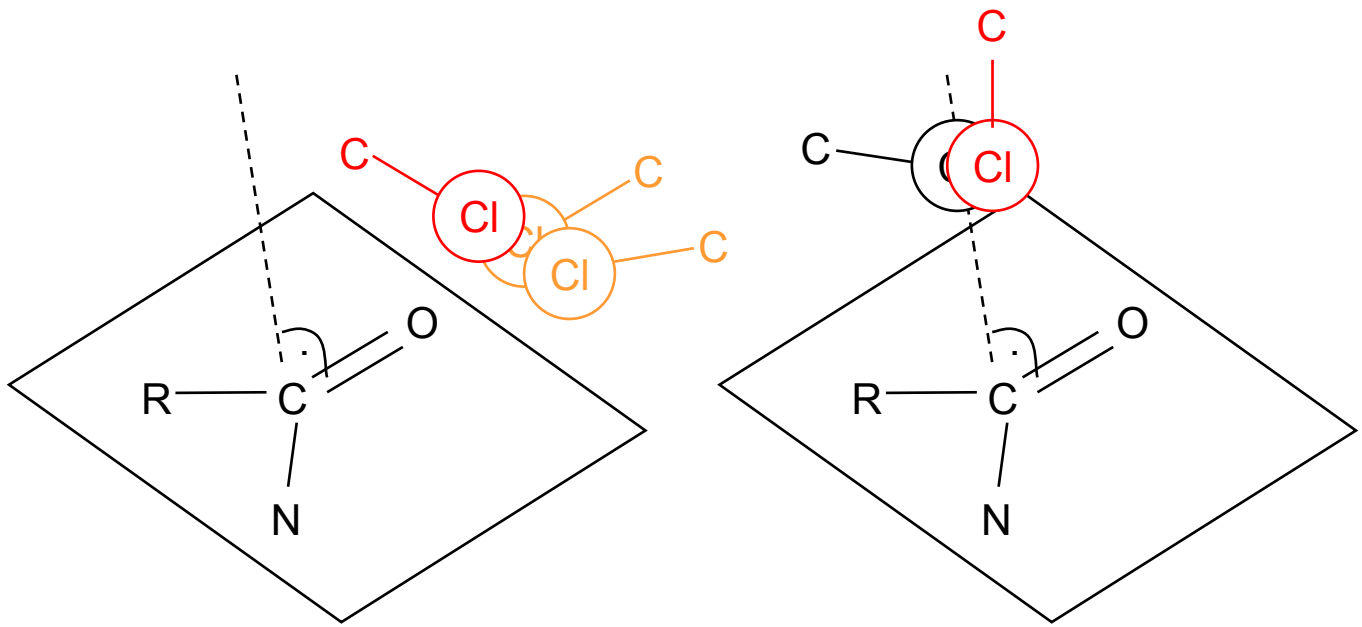
Cl-Amide Interactions

black: C...X distance < 3.6 Å
yellow: O...X distance < 3.3 Å
blue: both

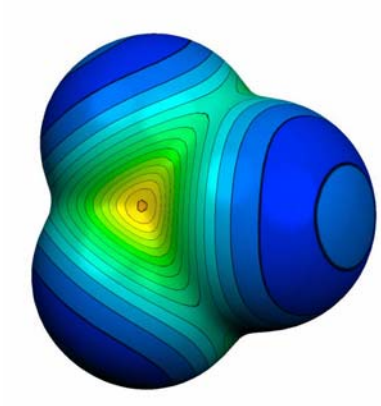




Observed Interaction Schemes



Rationalizing the Observed Interactions



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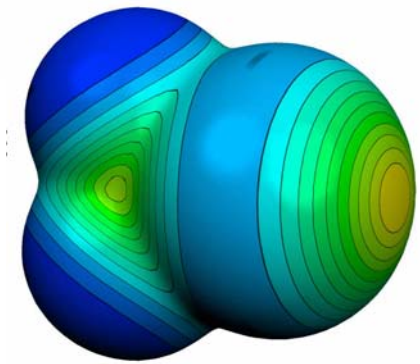
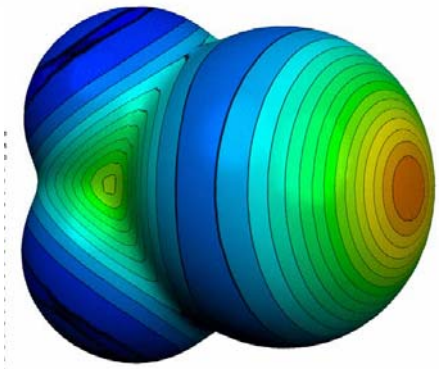


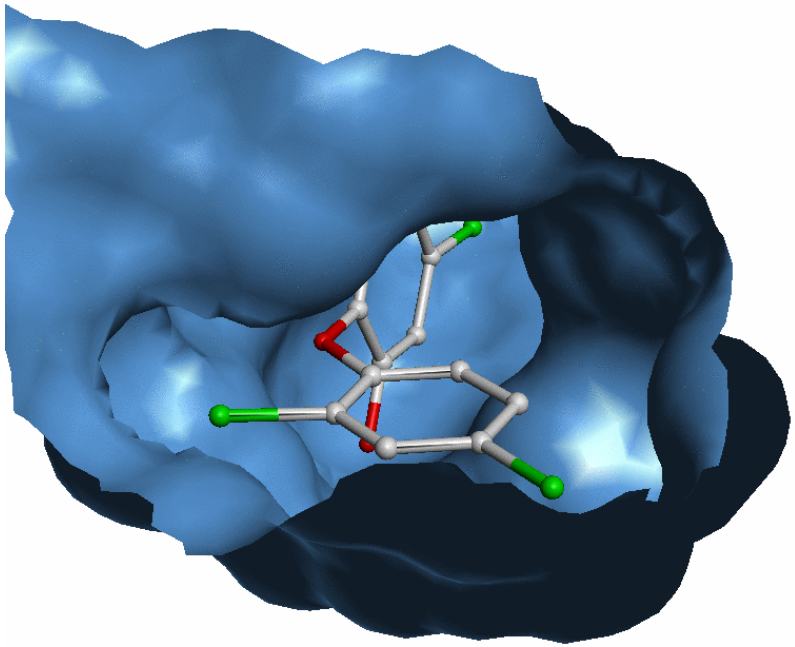
Cl



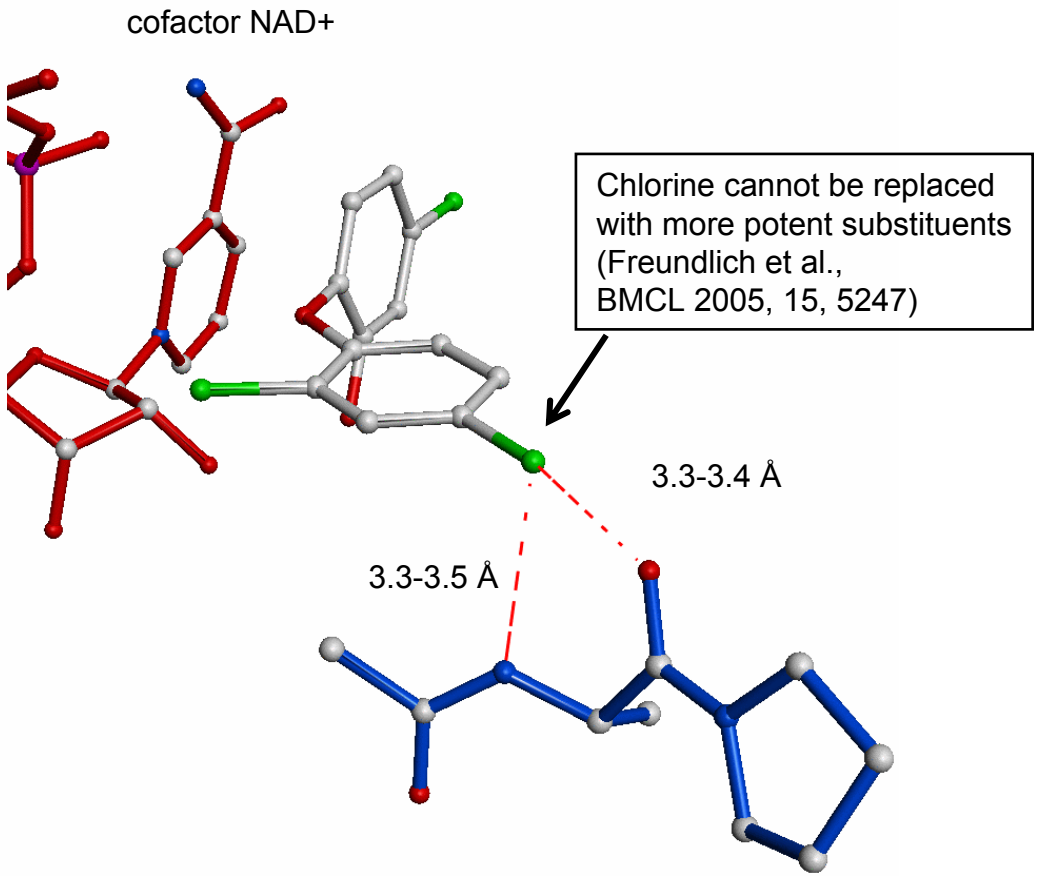
Br

Enoyl Reductase complexed with Triclosan

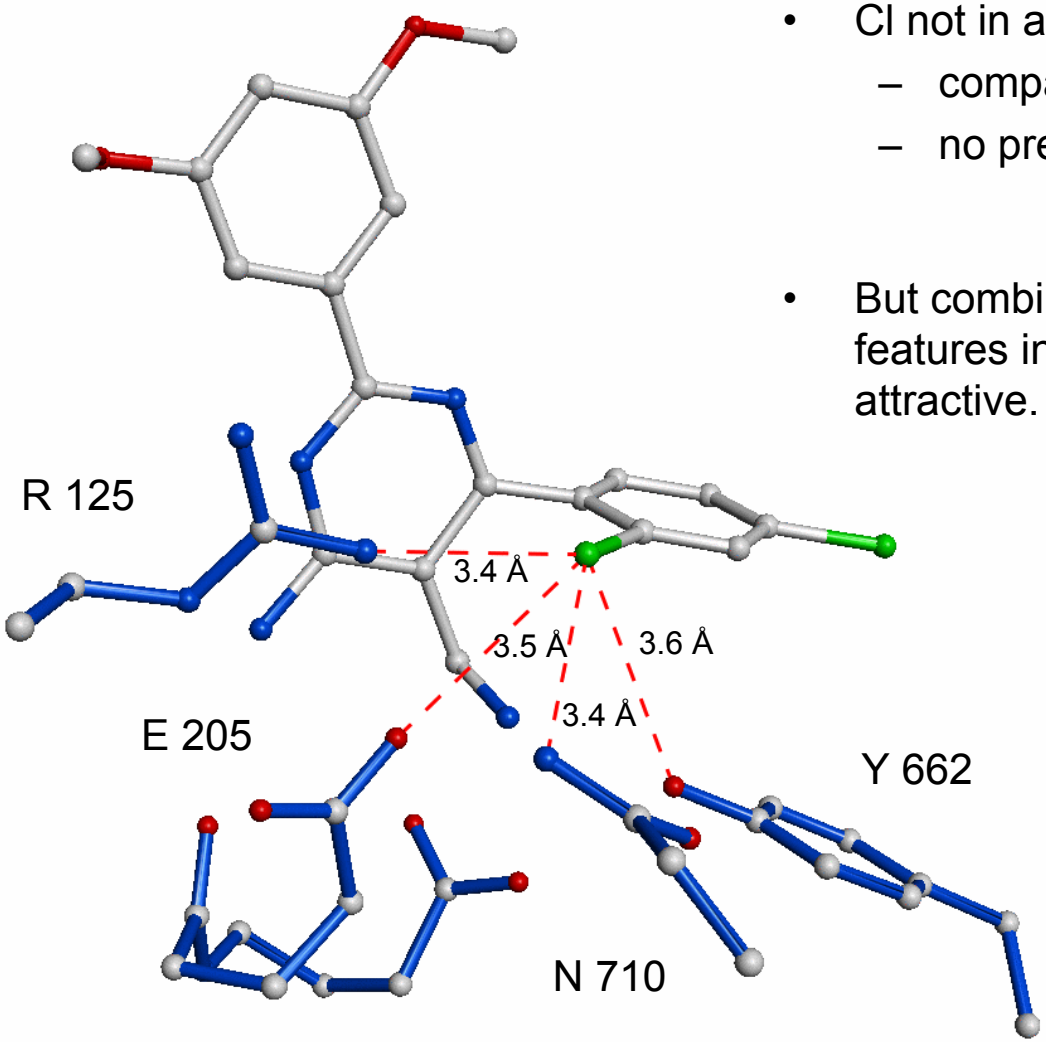
E.coli protein (1qsg)



Chlorine binds close to protein surface



Back to DPP-IV...



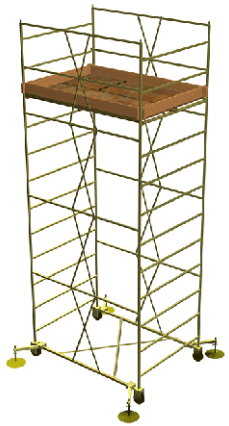
- Cl not in an optimal polar environment:
  - comparably long contact distances
  - no preferred angles

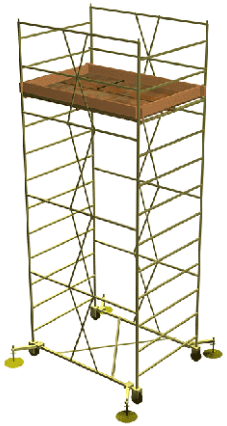
- But combination of Lewis basic and electrophilic features in environment makes interactions attractive.

Using Structural Databases

A New Tool for Scaffold Hopping

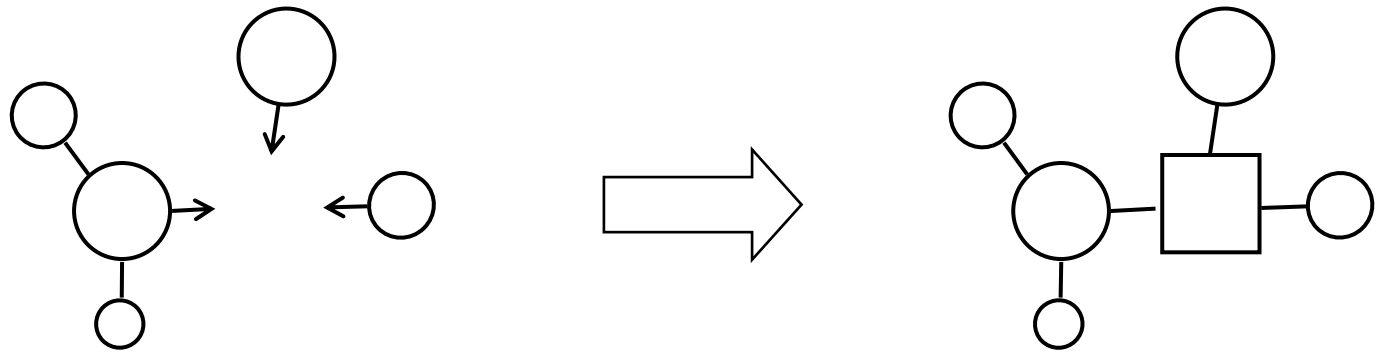
Target Family Approaches





A Computational Approach to Scaffold Hopping

Fragment Replacement



H.-J. Boehm et al. DDT Technologies 2004, 1, 217-224.

A New Implementation for an Old Idea

CAVEAT: A program to facilitate the design of organic molecules*

Georges Lauri and Paul A. Bartlett**

Department of Chemistry, University of California, Berkeley, CA 94720, U.S.A.

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Accepted 1 October 1993

Key words: Drug design; Database searching; CAVEAT; Ligand design

SUMMARY

A frequently encountered problem in the design of enzyme inhibitors and other biologically active molecules is the identification of molecular frameworks to serve as templates or linking units that can position functional groups in specific relative orientations. The program CAVEAT was designed to address this problem by searching 3D databases for such molecular fragments. Key innovations introduced in CAVEAT are a focus on relationships between bonds and the provision of automated methods to identify and classify structural frameworks. Performance has been a particular concern in formulating CAVEAT, since it is intended to be used in an interactive manner. The focus in this report is the design and implementation of the principal algorithms and the performance achieved.

Principles of CAVEAT:

- Replaces fragments of molecules given at least two exit vectors of a scaffold
- A pair of exit vectors defines a distance, two angles and a dihedral angle.
- Databases of 3D structures are converted to databases of binned vector pairs.
- No differentiation between types of bonds

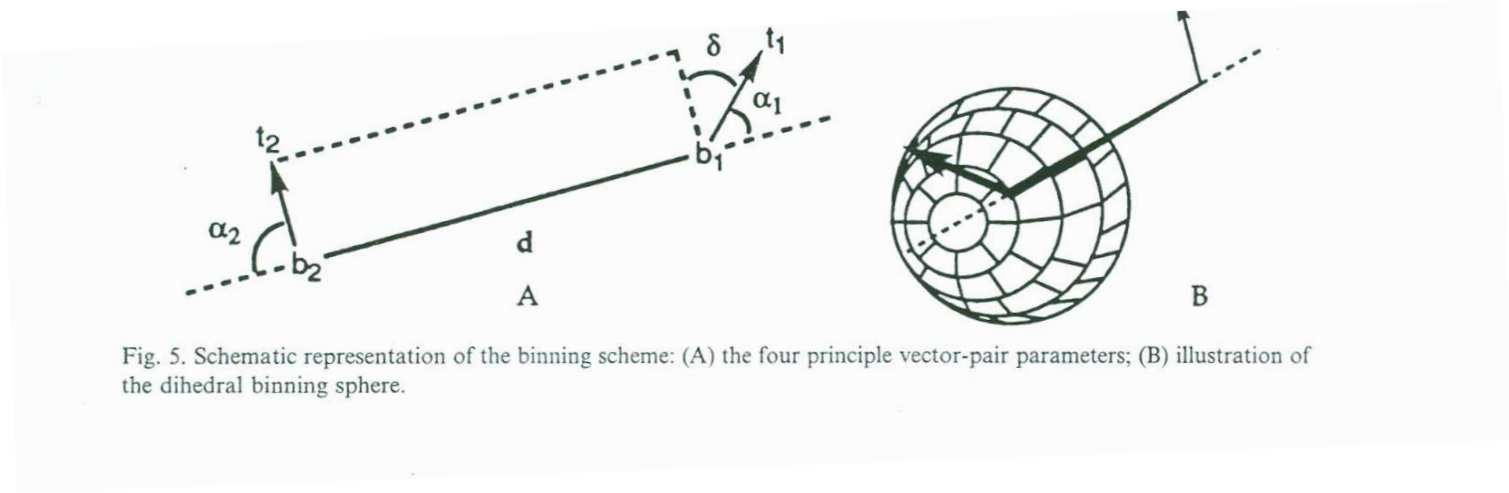
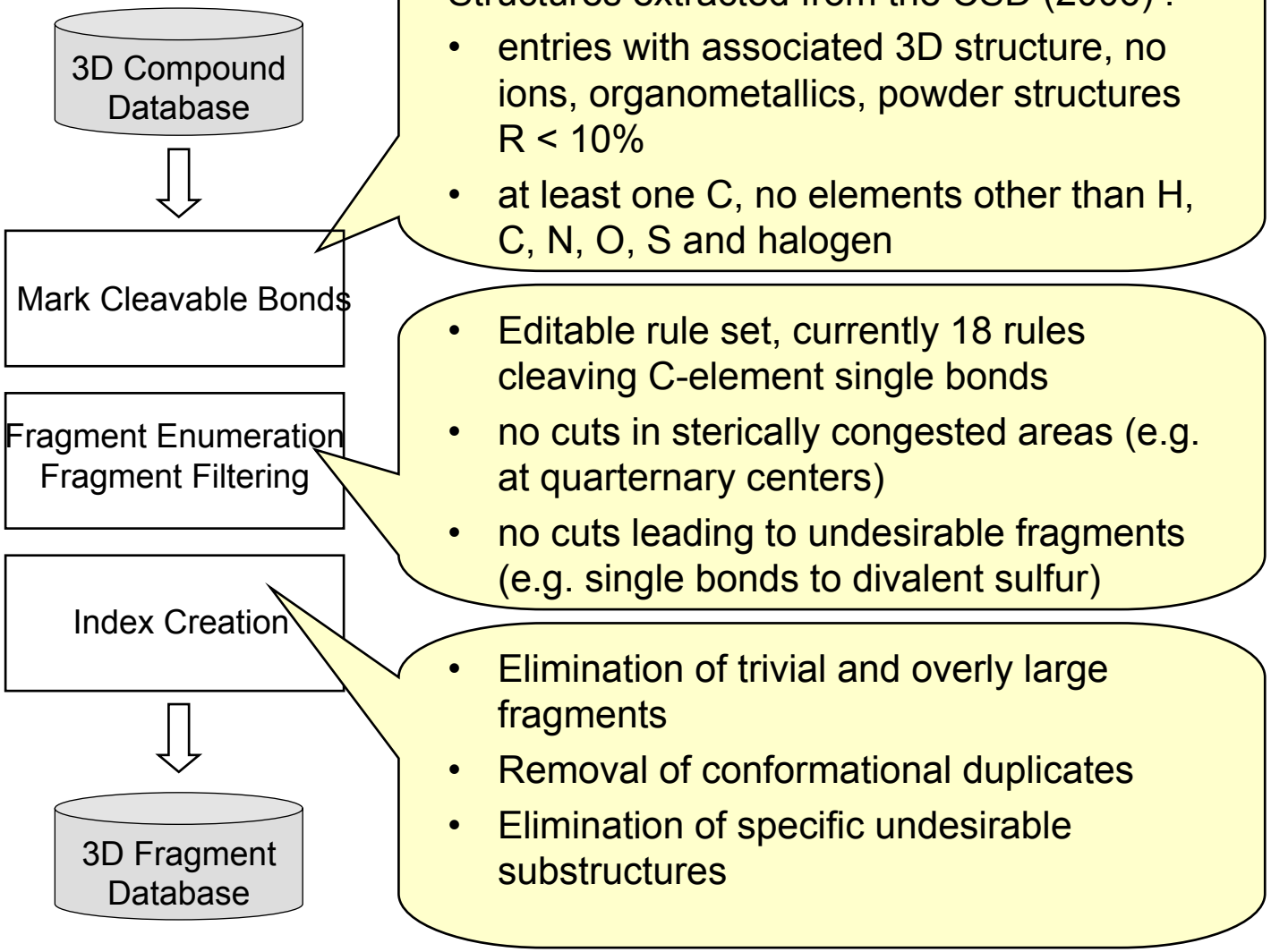
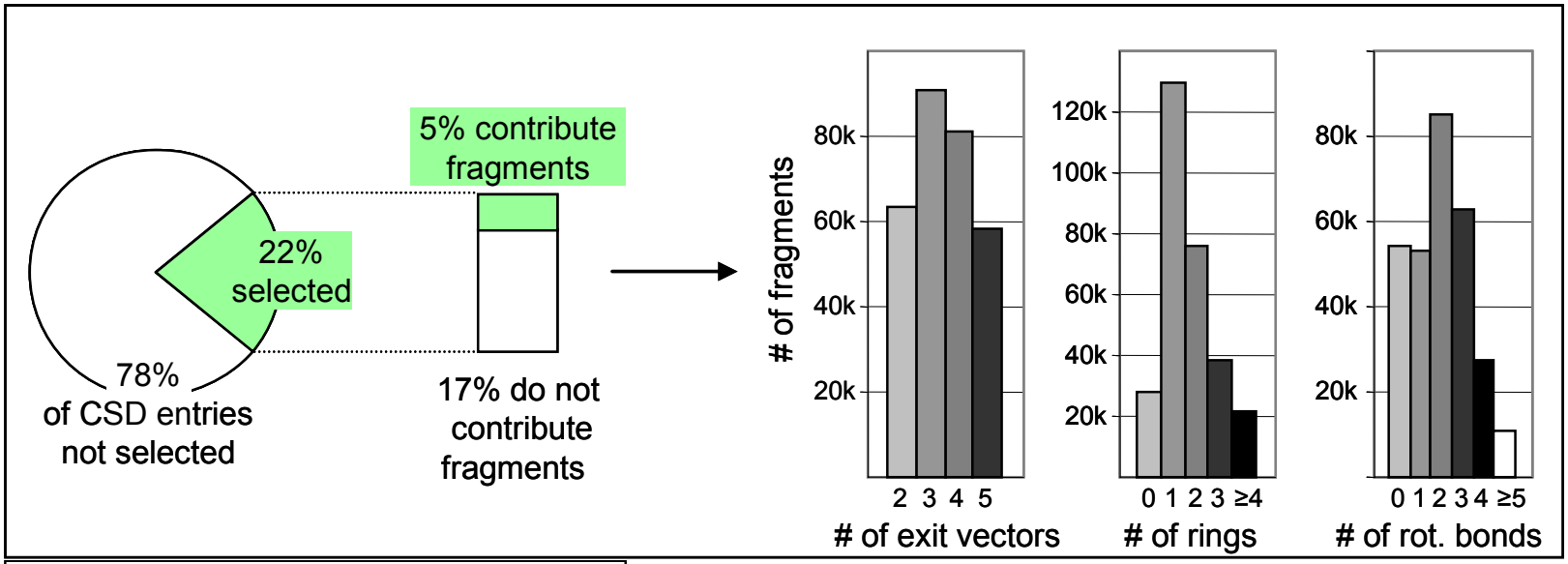


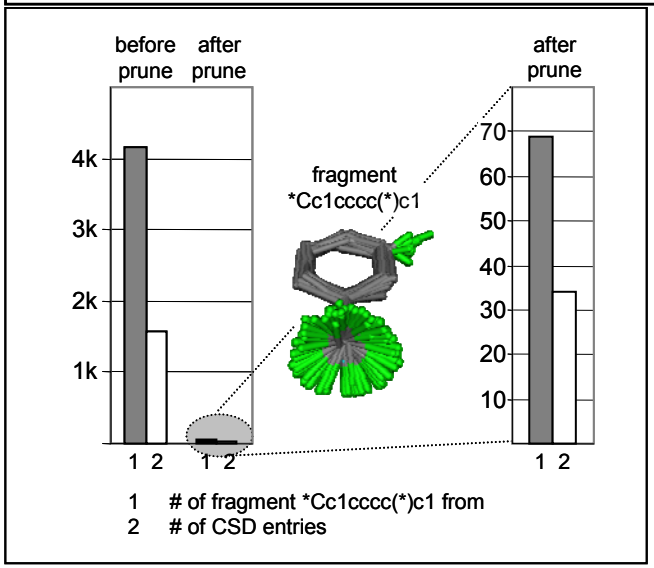
Fig. 5. Schematic representation of the binning scheme: (A) the four principle vector-pair parameters; (B) illustration of the dihedral binning sphere.

RECORE Preprocessing
Database Generation

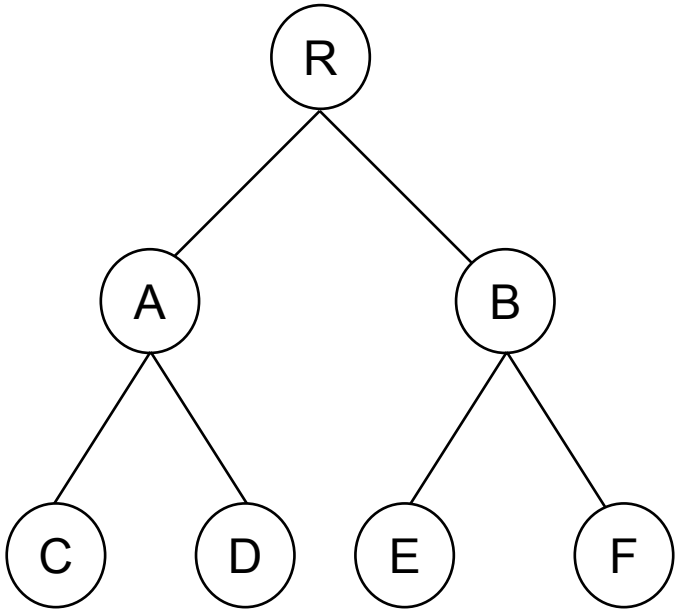


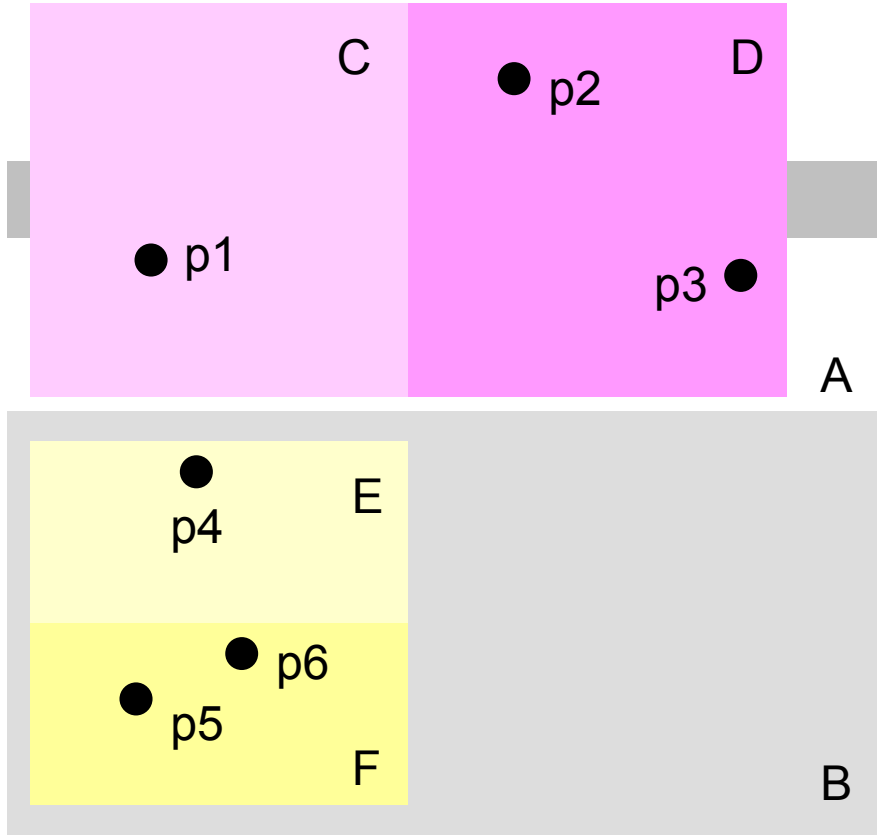
RECORE Preprocessing
Fragment Filtering



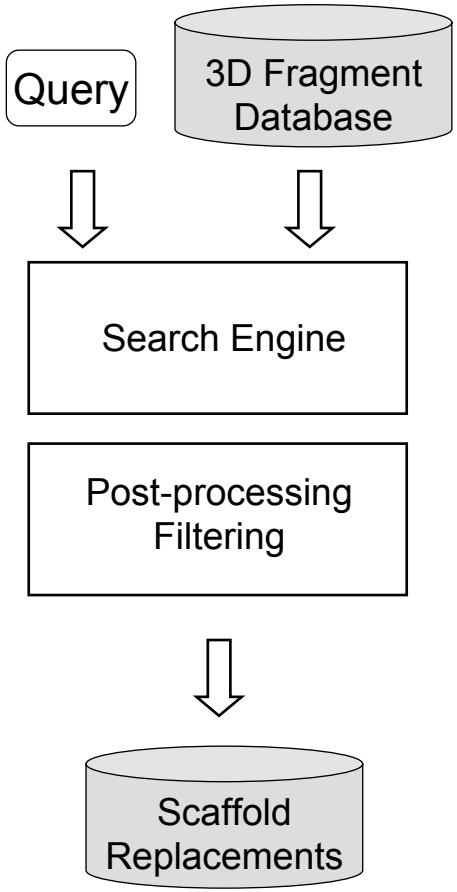


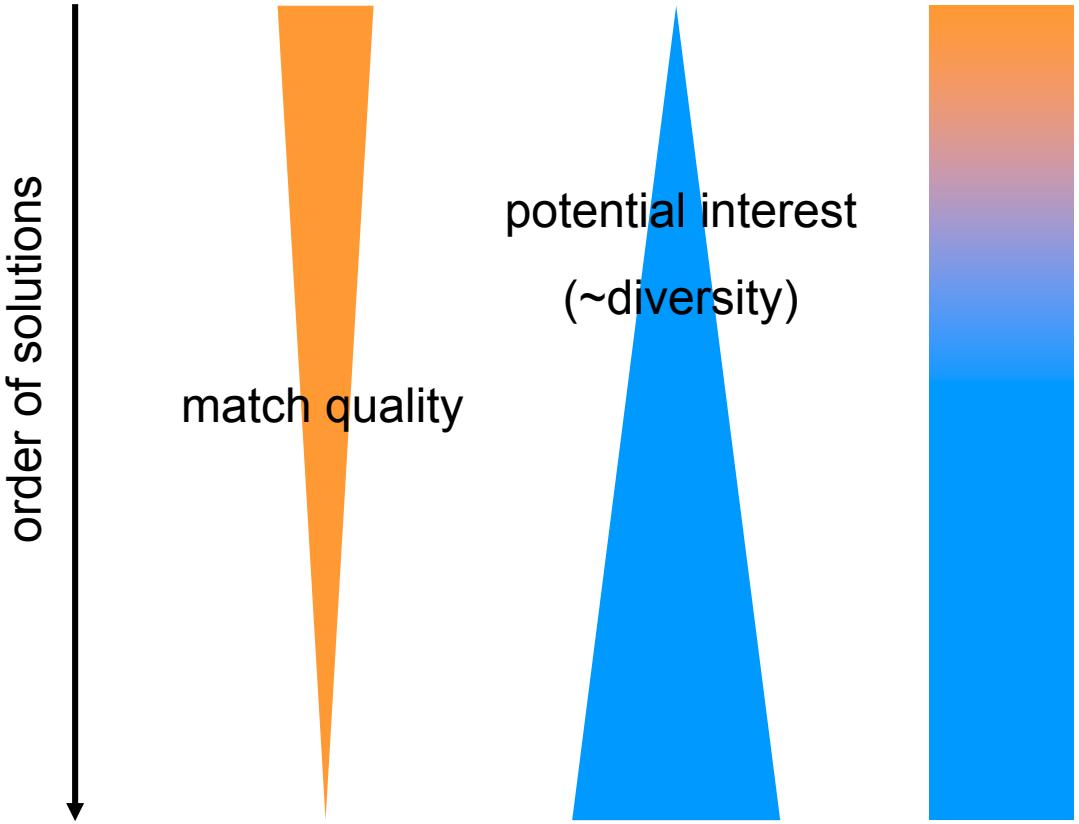
RECORE Preprocessing
Index Creation



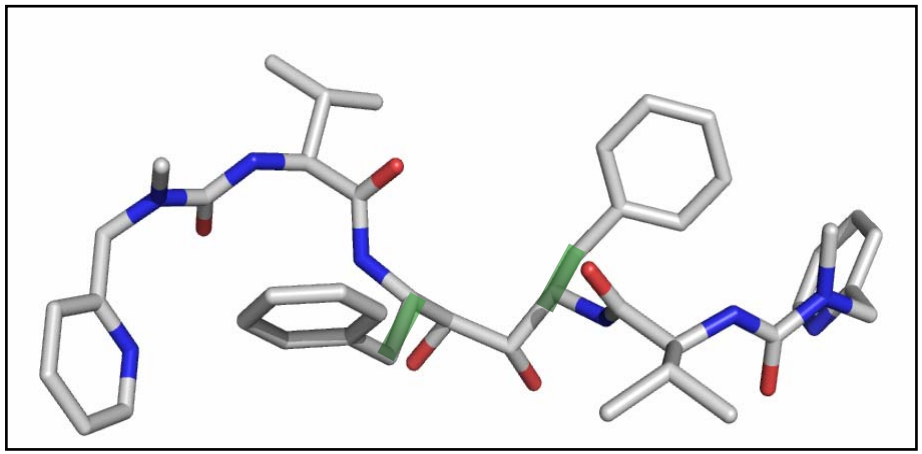


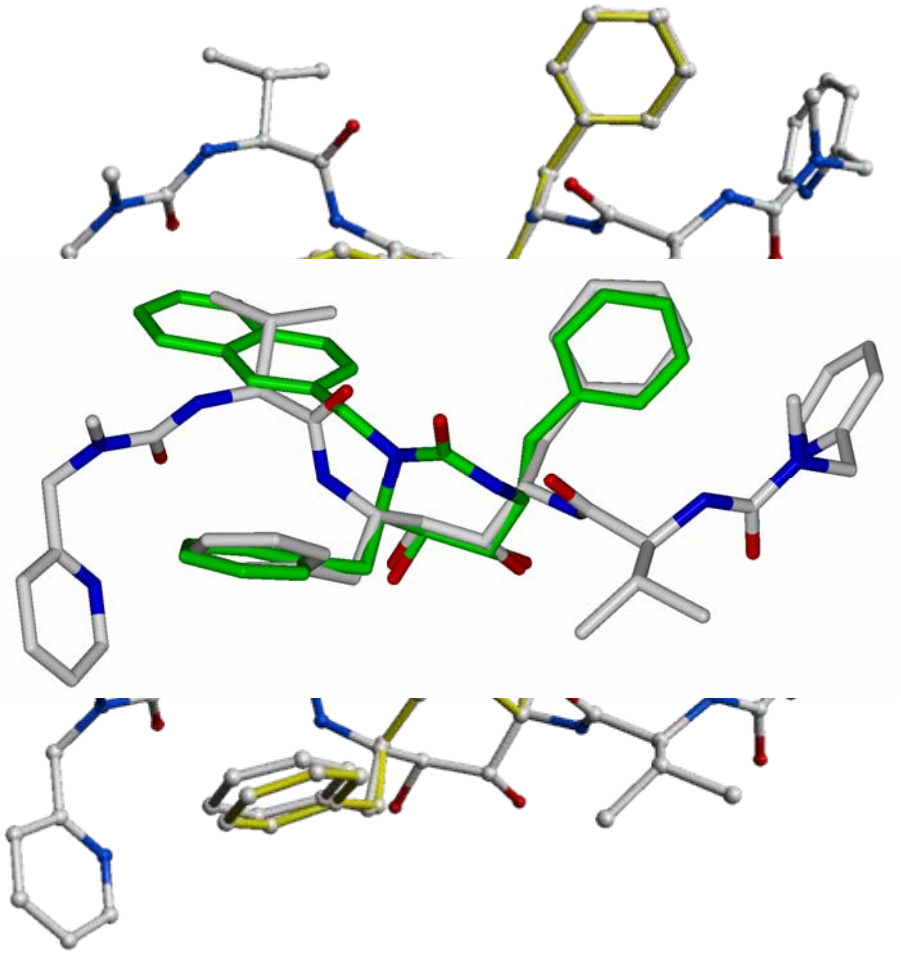
RECORE Output
Finding the Right Balance



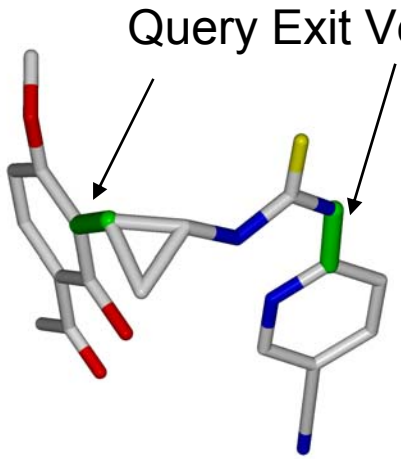


RECORE: Application Examples
HIV-Protease

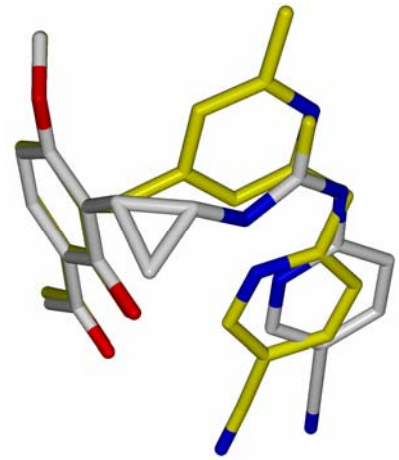




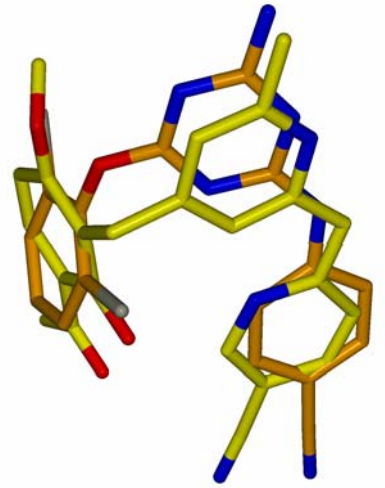
RECORE: Application Examples
HIV-RT



HIV-RT
MSC194



yellow:
solution based on
CSD structure CABVAD



orange:
JANSSEN-R129385

Roche

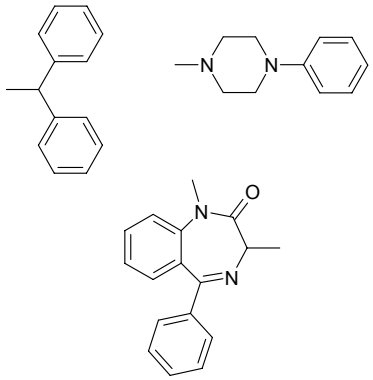
Using Structural Databases

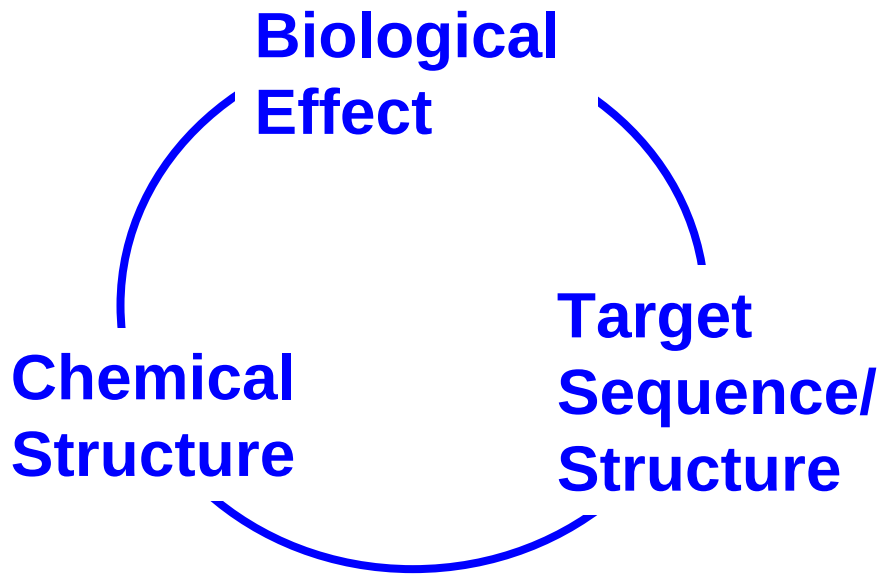
A New Tool for Scaffold Hopping

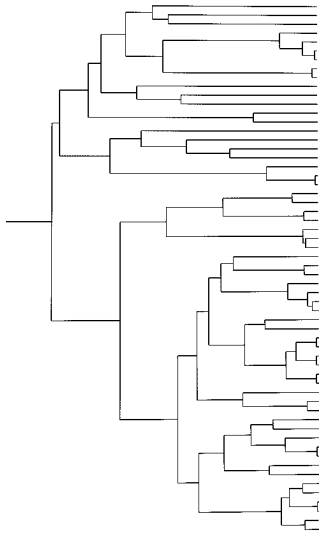
Target Family Approaches

Chemicogenomics – Making Sense of Data

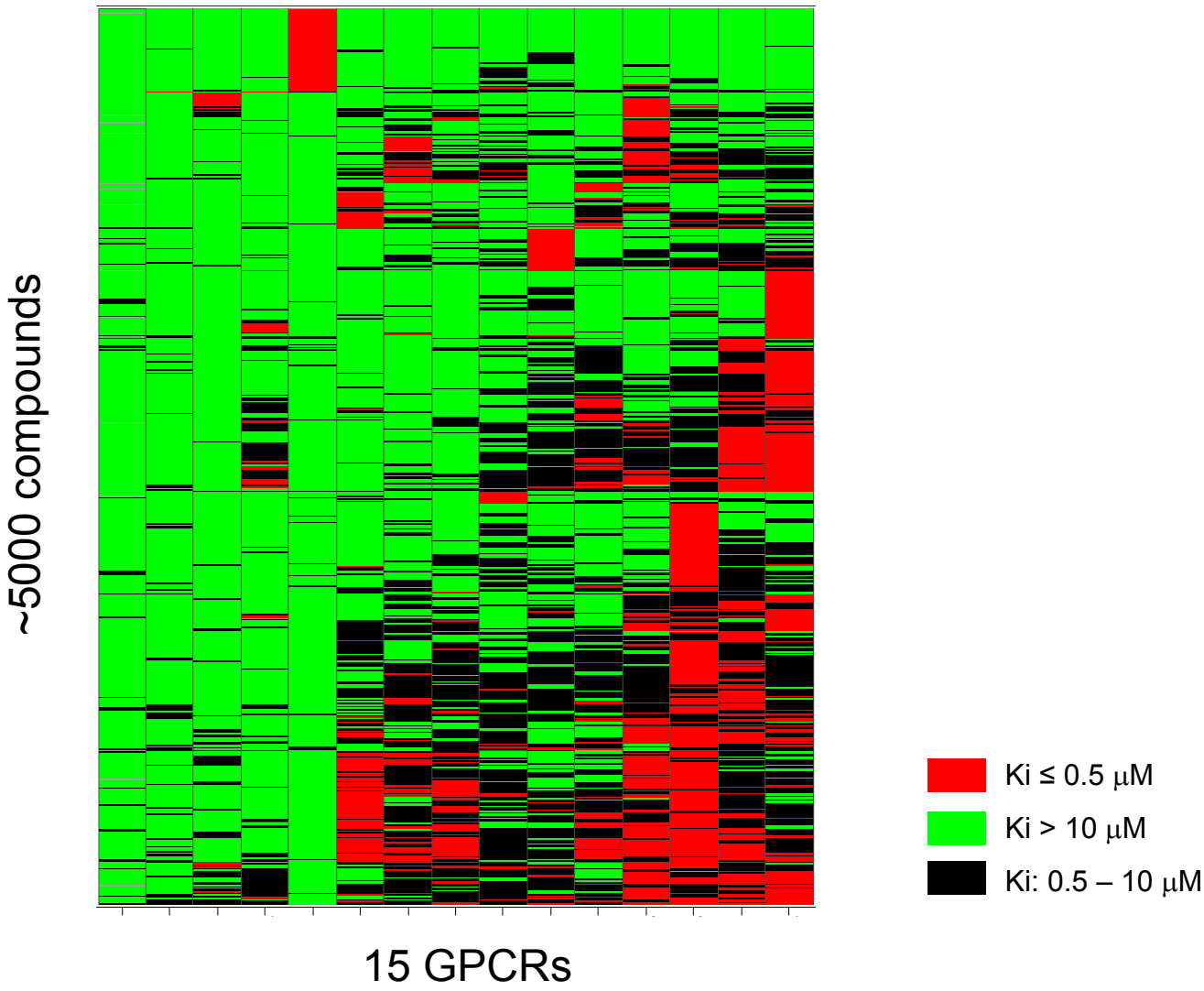
	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	R11	R12	R13	R14	R15
L1	6.1	7.1	4.7	8.8	7.2	6.9	7.7	5.4	5.6	4.0	4.2	4.5	5.5	4.2	4.6
L2	7.0	4.4	4.2	4.3	4.9	5.8	5.8	6.1	4.4	4.0	4.8	7.7	4.8	4.2	4.1
L3	5.6	4.4	4.2	4.8	4.4	6.5	6.0	5.7	5.1	4.0	5.3	7.7	5.8	4.2	4.1
L4	6.3	5.0	4.2	4.3	4.4	6.1	4.8	5.5	4.4	4.7	5.0	5.7	5.4	4.6	4.1



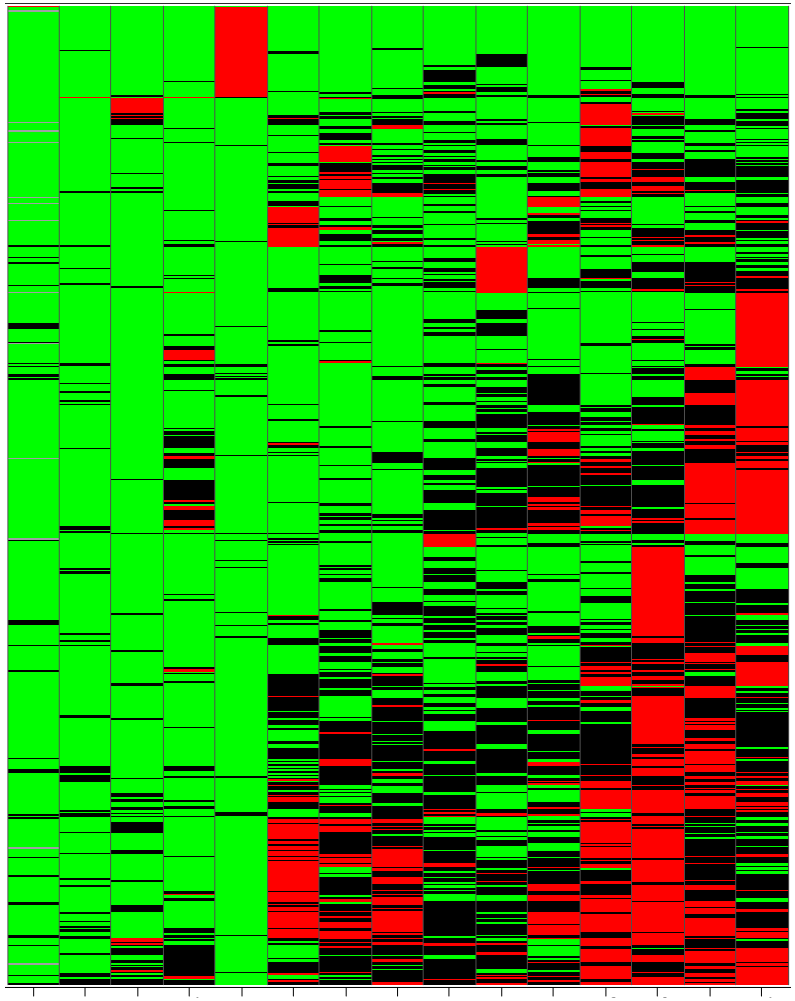




Panel Screen – A First Look



Mining for Leads – Search Type 1



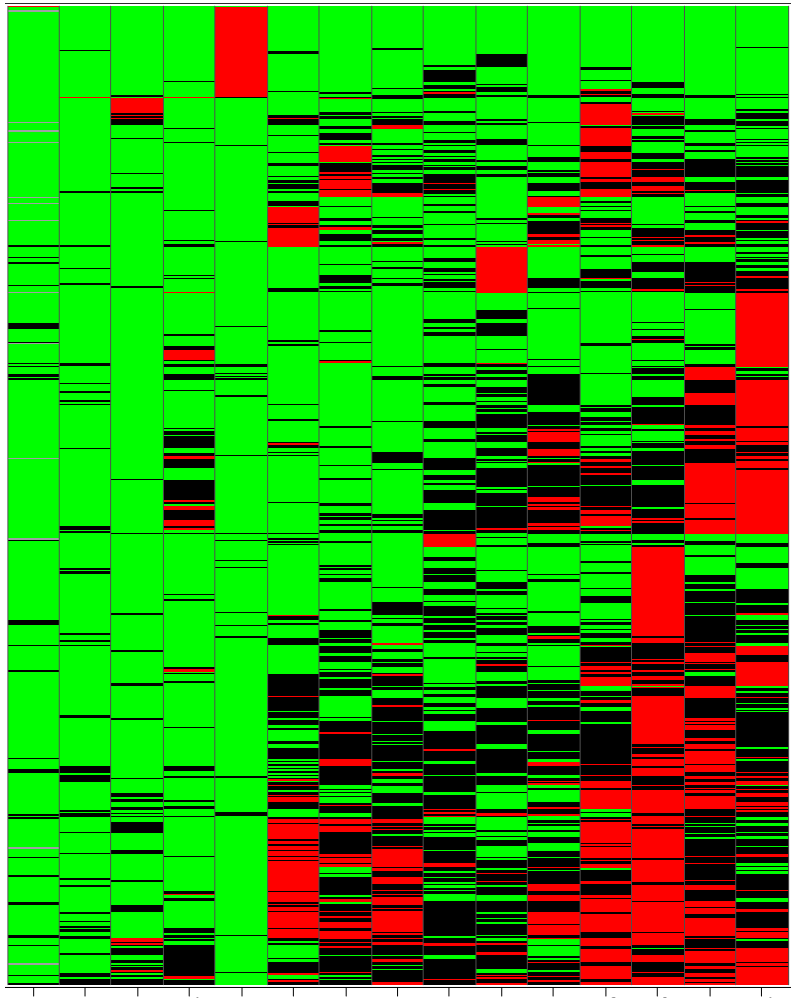
Receptor X

find closest neighbors in GPCR panel

5h2c_human	1	35	SIMSWIDVFSTIVGSAFLFWFFNFVWGYFTTCVLD
d3dr_human	1	35	SYMVFVDVMCTIVSSSFFFWFFHTTWGYTTVCSIN
hh1r_human	1	35	VLMNWLDYASTIWTANFTFWYFFTIWGYVDKCETF
oprk_human	1	35	VYPSVIDYNMFIVVFAFVFWIHICIAGYDIECSLF
Receptor X	1	35	LYPAVMDGNQFVMTAGFLFWFFNVVISYVGTCNAW

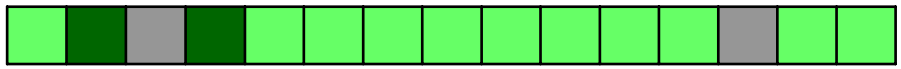
look up compounds binding to neighbors

Mining for Leads – Search Type 2



compound C
active at receptor X

determine affinity profile of C
and chemically similar compounds

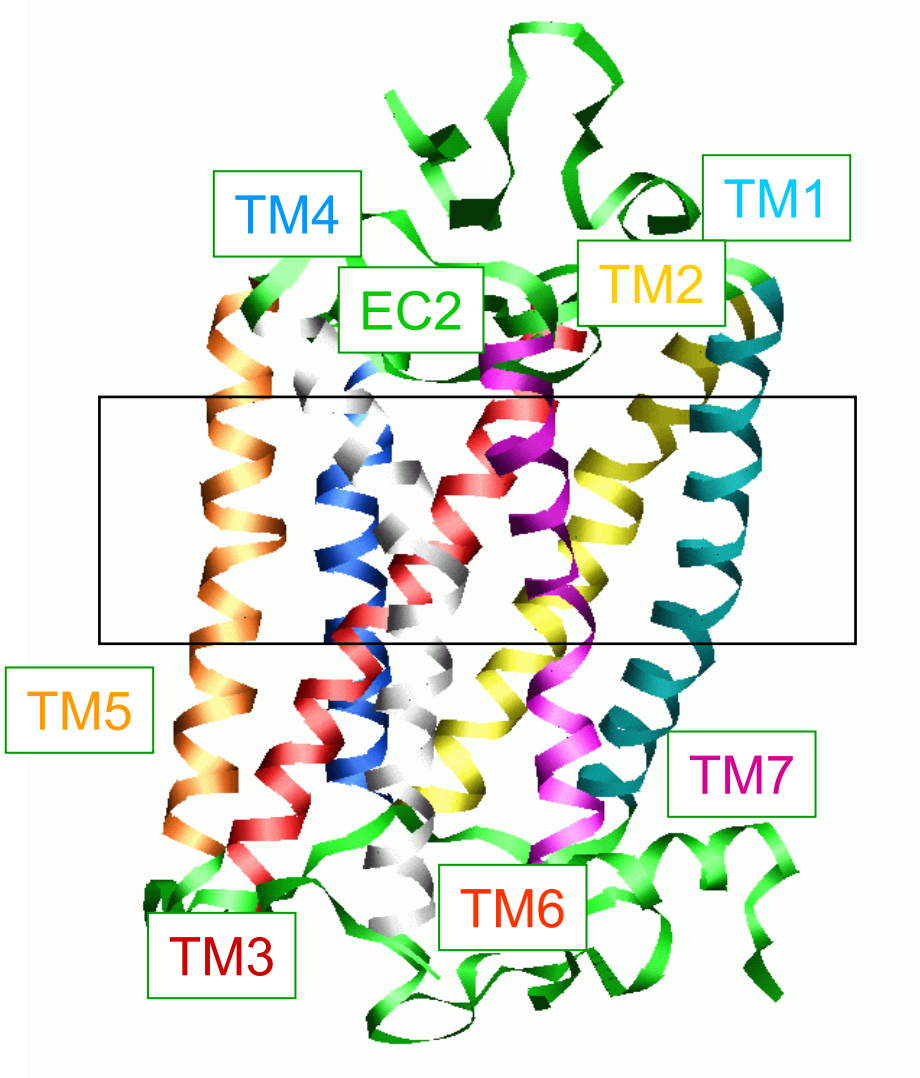


X

from panel, select
compounds with similar
affinity profile

One Structure for an Entire Target Class

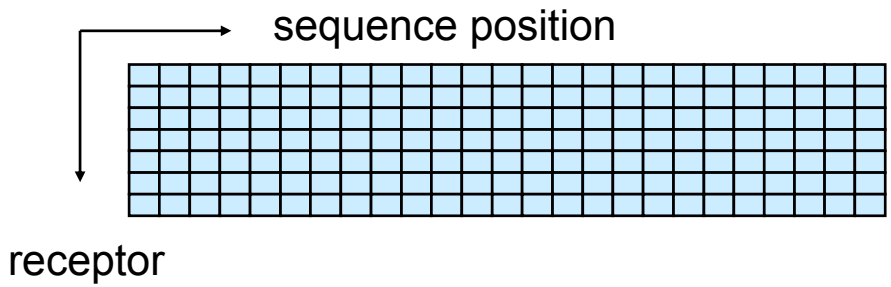
Opsd_bovin (PDB code 1f88)

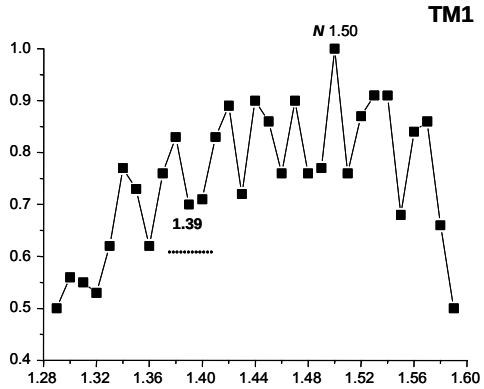


TM pocket for binding agonists / antagonists or allosteric modulators depending on subclass

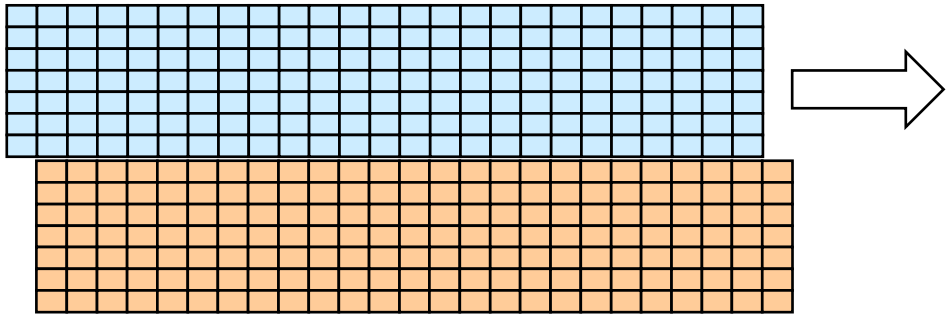
Alignment by Conservation Index

1. Align TM helices within a GPCR class





2. Align TM helix blocks to those of other GPCR classes



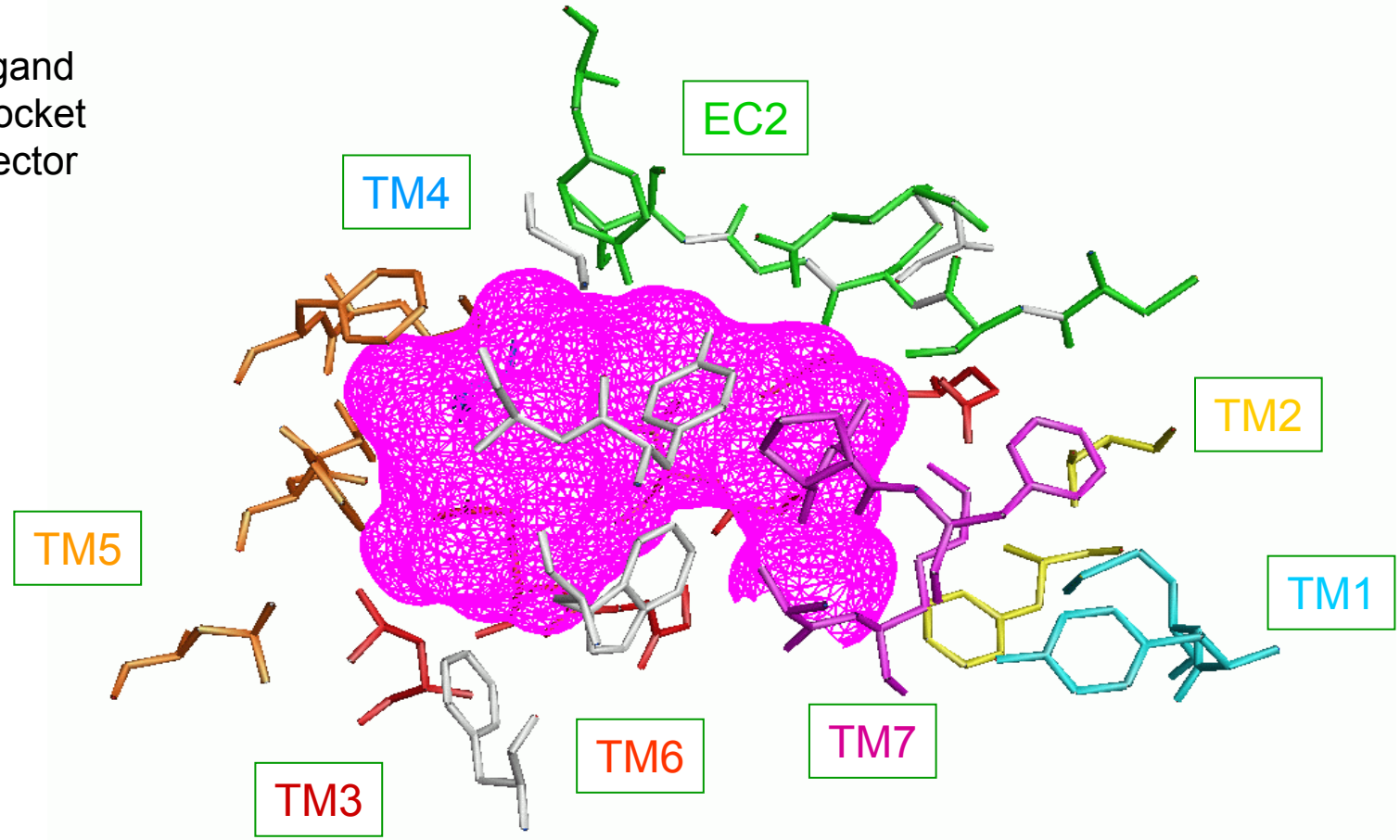
3. Extract binding pocket sequences to focus on less well conserved residues

N. Kratochwil et al. J. Chem. Inf. Model **2005**, *45*, 1324-1336.

Extracting the Transmembrane Pocket

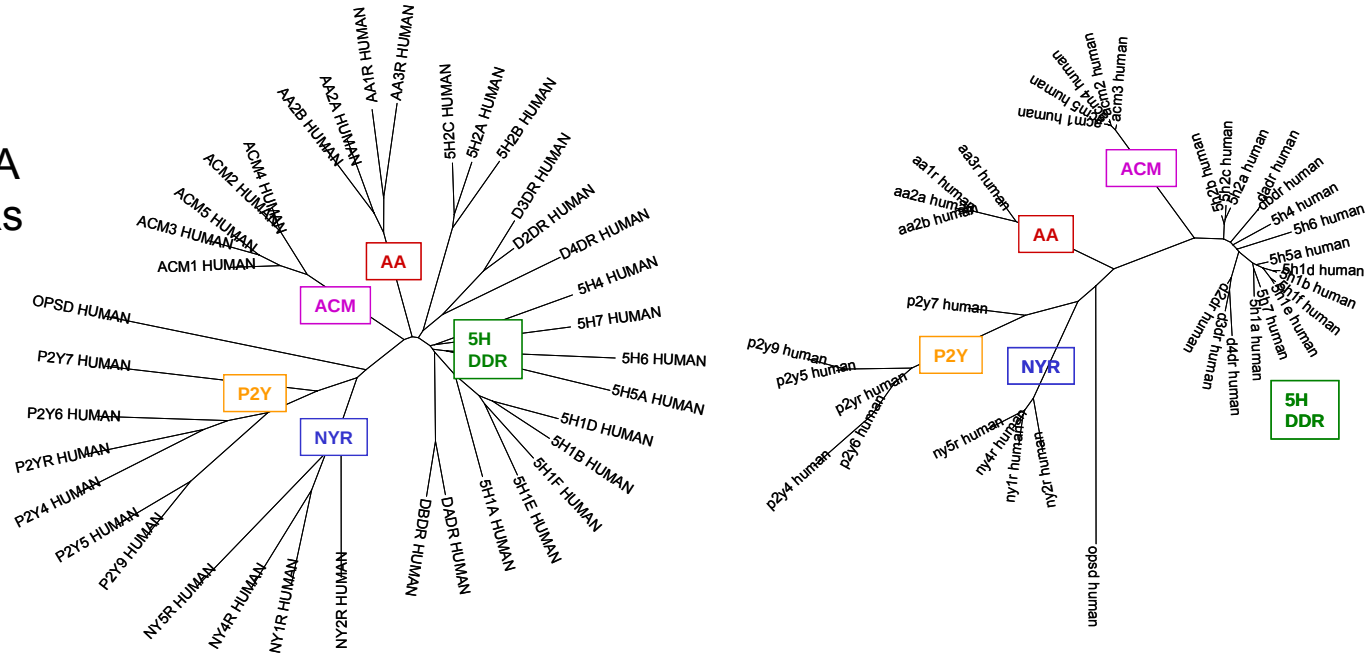
1.38
1.39
2.58
2.61
3.28
3.29
3.32
3.33
3.35
3.36
3.37
3.4
4.56
5.42
5.43
5.46
5.47
5.51
6.44
6.48
6.51
6.52
6.55
7.38
7.39
7.4
7.42
7.43
45.44
45.48
45.49
45.50
45.51
45.52
45.54

ligand pocket vector



Full Sequences versus Ligand Pocket Vectors

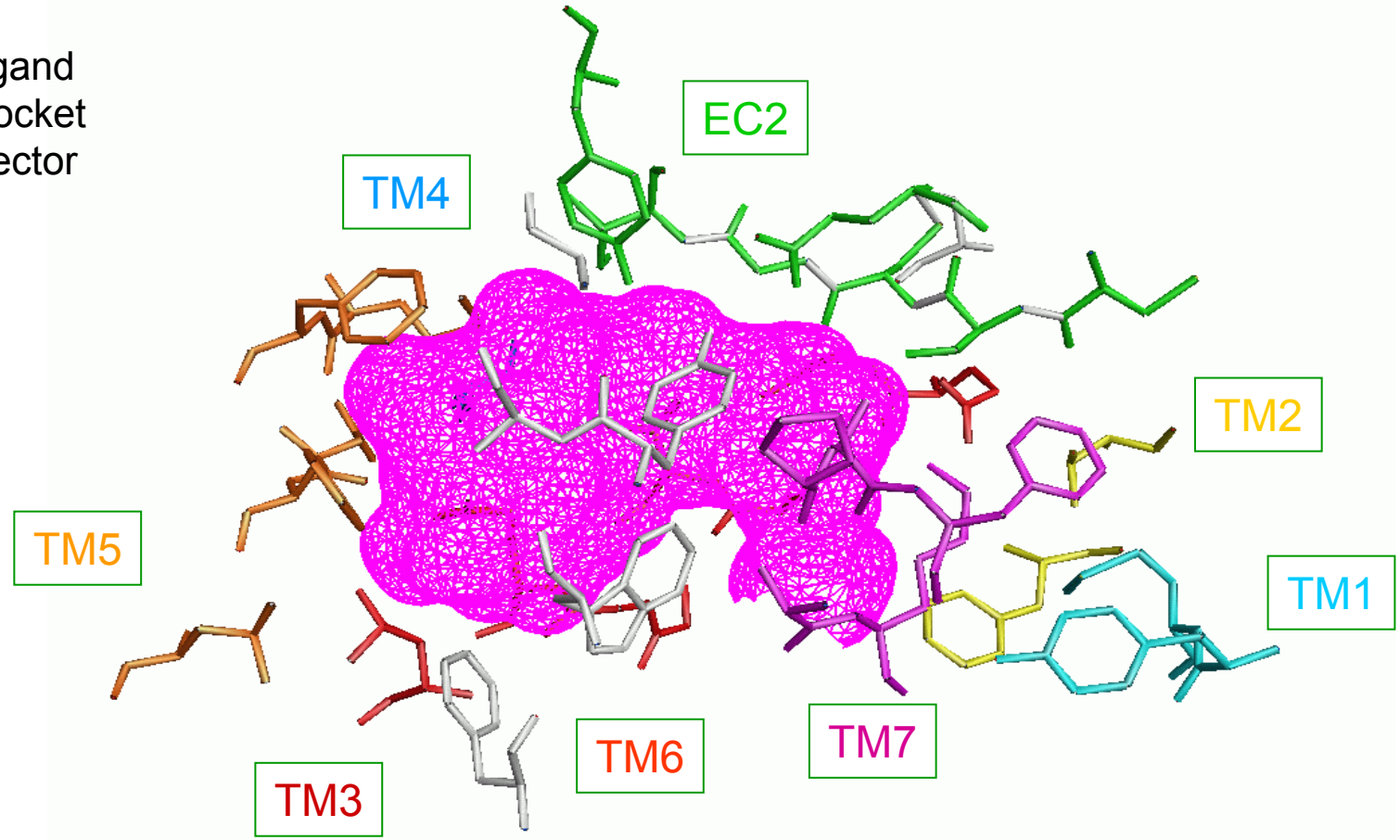
class A GPCRs



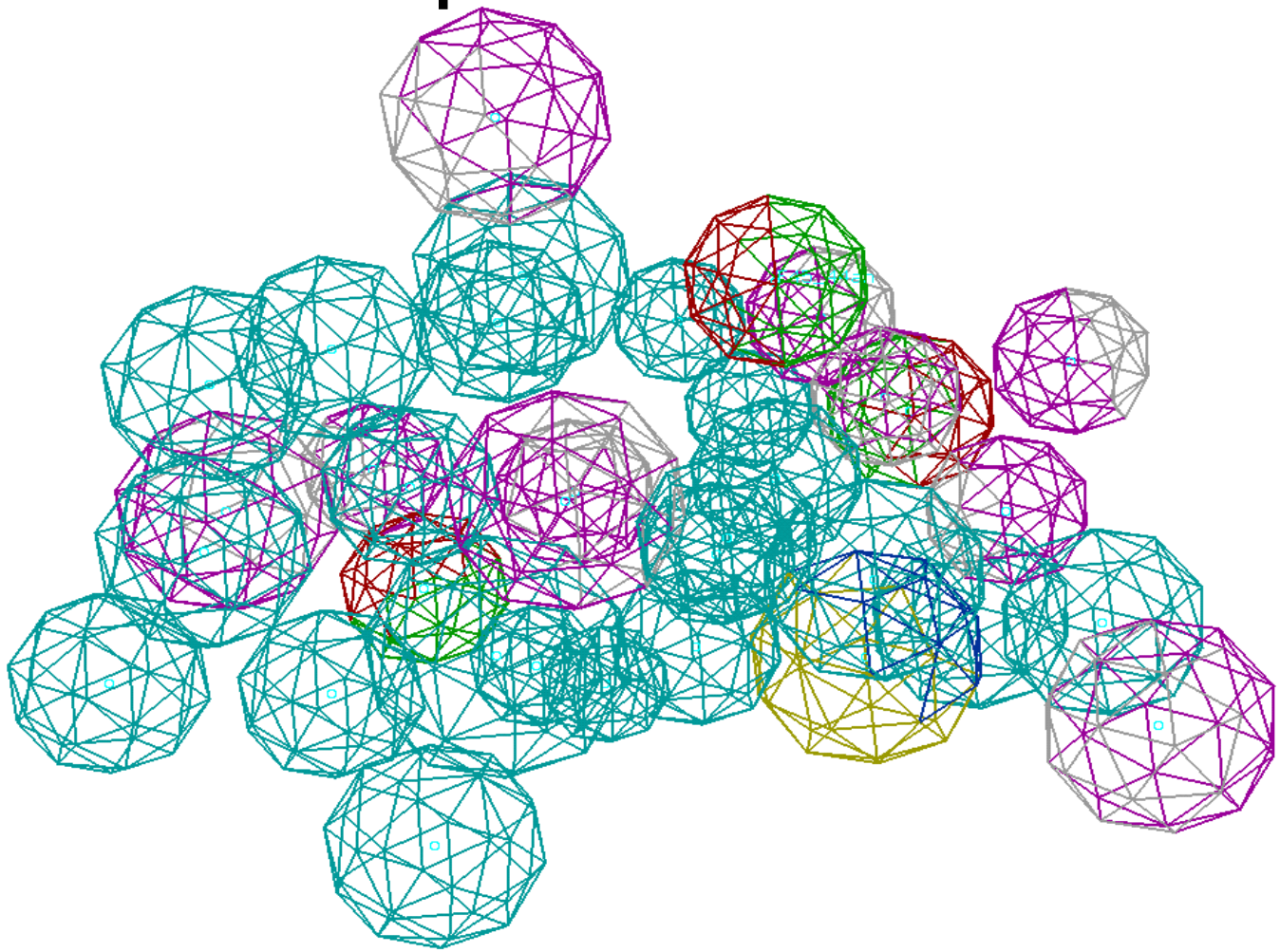
Extracting the Transmembrane Pocket

1.38
1.39
2.58
2.61
3.28
3.29
3.32
3.33
3.35
3.36
3.37
3.4
4.56
5.42
5.43
5.46
5.47
5.51
6.44
6.48
6.51
6.52
6.55
7.38
7.39
7.4
7.42
7.43
45.44
45.48
45.49
45.50
45.51
45.52
45.54

ligand pocket vector



Receptor-based Pharmacophore Models



- Acceptor /Negative
- Donor /Positive
- Donor
- Hydrophobic (R/L)
- Donor/Acceptor
- Acceptor

Feature position and radii according to rotamer library

Lovell, S.C. et al., Proteins 2000, 40, 389-408

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